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Coma Prognostication After Acute Brain Injury
A Review

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IMPORTANCE Among the most impactful neurologic assessments is that of neuroprognostication, defined here as the prediction of neurologic recovery from disorders of consciousness caused by severe, acute brain injury. Across a range of brain injury etiologies, these determinations often dictate whether life-sustaining treatment is continued or withdrawn; thus, they have major implications for morbidity, mortality, and health care costs. Neuroprognostication relies on a diverse array of tests, including behavioral, radiologic, physiological, and serologic markers, that evaluate the brain's functional and structural integrity.

OBSERVATIONS Prognostic markers, such as the neurologic examination, electroencephalography, and conventional computed tomography and magnetic resonance imaging (MRI), have been foundational in assessing a patient's current level of consciousness and capacity for recovery. Emerging techniques, such as functional MRI, diffusion MRI, and advanced forms of electroencephalography, provide new ways of evaluating the brain, leading to evolving schemes for characterizing neurologic function and novel methods for predicting recovery.

CONCLUSIONS AND RELEVANCE Neuroprognostic markers are rapidly evolving as new ways of assessing the brain's structural and functional integrity after brain injury are discovered. Many of these techniques remain in development, and further research is needed to optimize their prognostic utility. However, even as such efforts are underway, a series of promising findings coupled with the imperfect predictive value of conventional prognostic markers and the high stakes of these assessments have prompted clinical guidelines to endorse emerging techniques for neuroprognostication. Thus, clinicians have been thrust into an uncertain predicament in which emerging techniques are not yet perfected but too promising to ignore. This review illustrates the current, and likely future, landscapes of prognostic markers. No matter how much prognostic markers evolve and improve, these assessments must be approached with humility and individualized to reflect each patient's values.

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Disorders of consciousness (DoC) caused by severe, acute brain injury present numerous challenges to clinicians and families. Among the most difficult is the problem of neuroprognostication, or the prediction of neurologic recovery,[1] which often dictates whether life-sustaining treatment (LST) is continued or withdrawn—a poor neurologic prognosis may prompt discontinuation of LST, leading to the patient's death.[2,3] Accuracy in neuroprognostication is therefore paramount, as error could result in avoidable morbidity and mortality.

DoC can be caused by several etiologies of acute brain injury (**Figure 1**), such as hypoxic-ischemic brain injury (HIBI), traumatic brain injury (TBI), intracranial hemorrhage, and ischemic stroke, each of which is associated with its own prognostic markers. However, there are fundamental principles of prognostication that generalize across etiologies.[1] The first step in neuroprognostication is determining the patient's current level of consciousness, or neurologic function (**Figure 2**A). The second step is to collect and synthesize data to anticipate a likely trajectory of neurologic recovery (Figure 2B). The third step is to assess the patient's goals of care, or what constitutes an acceptable level of neurologic recovery (Figure 2C). Finally, this information can be used to determine the probability of an acceptable or unacceptable outcome, which may then influence decisions about LST (Figure 2D).

Here, we review each of these components of neuroprognostication, outlining how consciousness and neurologic function are assessed, describing conventional and emerging prognostic markers (focusing on those endorsed by clinical guidelines[4-6] and expert opinion[7]; **Figure 3**), and discussing how prognostic data may inform decisions about LST. The field has made tremendous progress in characterizing the brain's potential for recovery and continues to advance our predictive accuracy. However, the prediction of future recovery will always be hampered by inherent uncertainty and thus must be approached comprehensively and humbly.

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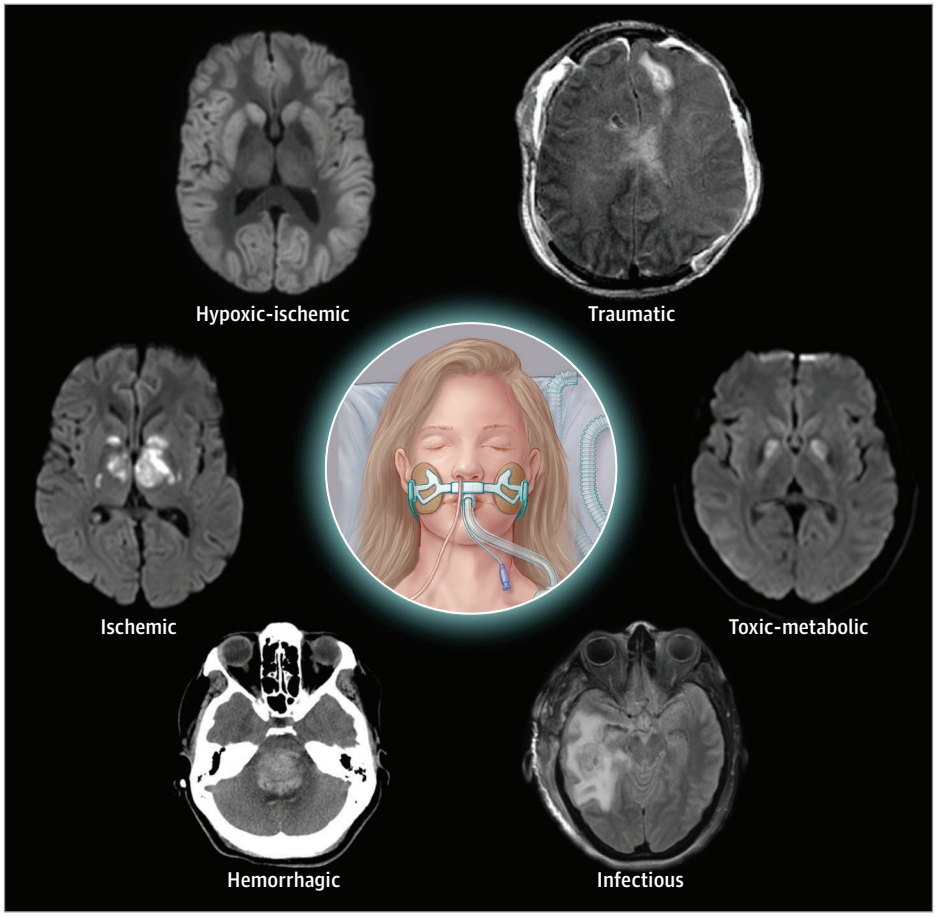
Figure 1. Brain Injury Etiologies of Disorders of Consciousness



Disorders of consciousness that require neuroprognostication can be caused by a variety of severe, acute brain injuries. Such etiologies include hypoxic-ischemic brain injury after cardiac arrest, traumatic brain injury, ischemic stroke, intracranial hemorrhage, encephalitis, and toxic-metabolic insults. Representative brain magnetic resonance images and computed tomographic scans are depicted for each of these etiologies.

Determining Current Level of Consciousness and Neurologic Function

Conventional Classification Schemes

The first step in neuroprognostication is evaluating the patient's current level of neurologic function (Figure 2A). Traditionally, such function has been framed in terms of consciousness, which comprises arousal (or wakefulness) and awareness (or the content of experience).[8] Levels of consciousness have conventionally been divided into discrete diagnostic categories: coma, in which patients lack both arousal and awareness; the vegetative state (VS) or unresponsive wakefulness syndrome (UWS), in which patients are awake but lack awareness; the minimally conscious state (MCS), in which patients are awake but only minimally or intermittently aware; and emergence from MCS (eMCS), in which patients have recovered functional communication or functional object use.[9] The MCS has been subdivided into MCS minus (MCS−; without language function) and MCS plus (MCS+; with language function).[10] Although historically some terms have conflated diagnosis and prognosis, such as the "permanent vegetative state," this terminology has been abandoned following reports of late consciousness recovery[11]; as such, existing diagnostic categories describe only the current state.[5]

These categories of DoC are conventionally evaluated with the Coma Recovery Scale–Revised (CRS-R),[12] a comprehensive behavioral assessment endorsed by clinical guidelines[4,5] that detects subtle signs of consciousness in up to 40% of patients who appear unresponsive on a standard examination (purposeful eye movements, such as visual fixation and pursuit, are conscious behaviors frequently overlooked by the standard examination).[13] However, the CRS-R requires expertise and time (up to 30 minutes) to administer, which may be prohibitive in the acute intensive care unit (ICU) setting. Thus, an abbreviated version—the CRS-R for Accelerated Standardized Testing (CRSR-FAST)[14]—and the Simplified Evaluation of Consciousness Disorders (SECONDs)[15] have been developed to rapidly provide equivalent sensitivity for detecting consciousness. The Glasgow Coma Scale (GCS)[16] is widely used in clinical practice and can be performed rapidly, but it is an insensitive measure of consciousness.[13,17] Other scales have been proposed, such as the Full Outline of Unresponsiveness (FOUR) score,[18] which includes detailed assessments of brainstem function, and the revised Motor Behavior Tool (MBT-r), which elicits signs of consciousness through emotionally salient stimuli.[19] Importantly, levels of consciousness in DoC commonly fluctuate, particularly in the ICU,[20] and therefore serial assessments may be necessary to sensitively detect periods of consciousness.[21]

Emerging Classification Schemes

Emerging technologies have complicated this diagnostic scheme and prompted development of new phenotypic categories. A subset of

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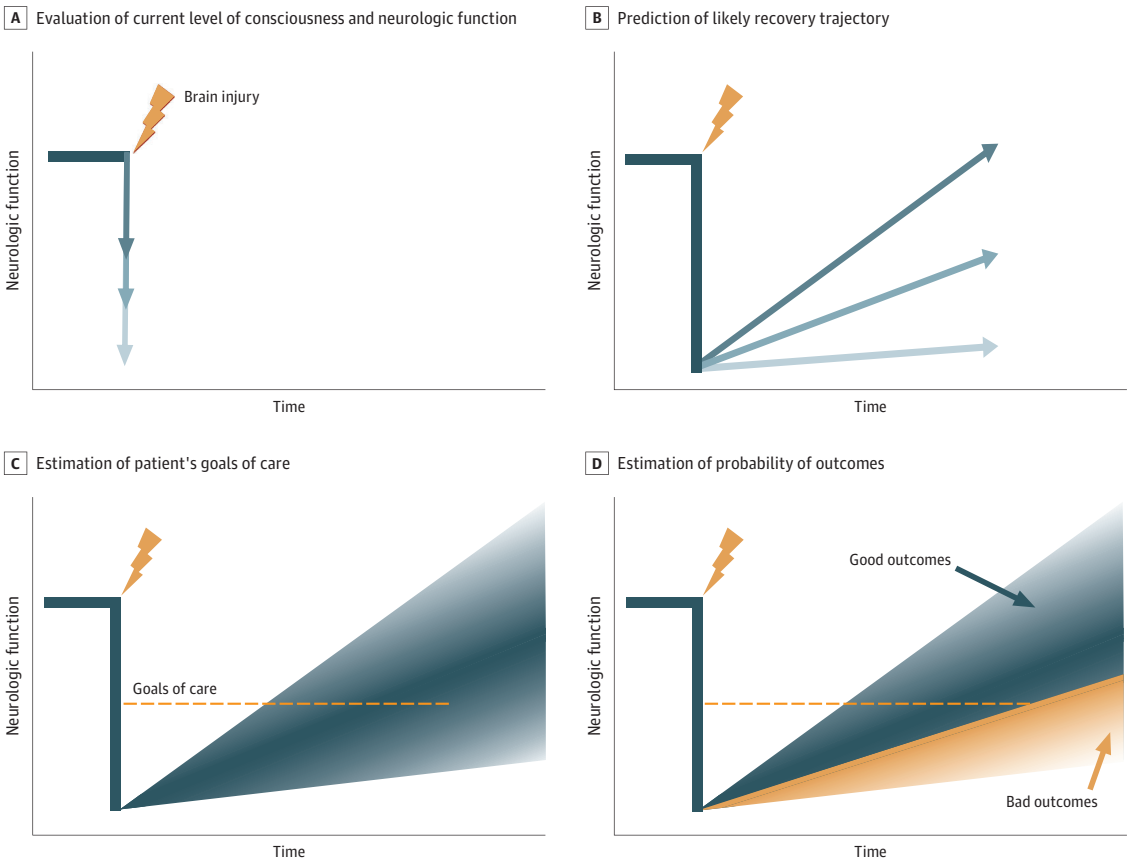
Figure 2. Principles of Neuroprognostication



Neuroprognostication comprises several steps, including the evaluation of a patient's current level of consciousness and neurologic function after acute brain injury (A), the prediction of a likely recovery trajectory (B), the estimation of a patient's goals of care (C), and the synthesis of these data to estimate the probability of acceptable and unacceptable outcomes (D).

patients who appear unresponsive on behavioral evaluation can willfully modulate their brain activity to command, a phenomenon termed *cognitive motor dissociation* (CMD) or *covert consciousness*.[22] CMD was first identified in 2006 with task-based functional magnetic resonance imaging (fMRI), which detects brain activity by measuring the accompanying blood-oxygen-level-dependent (BOLD) signal: a behaviorally unresponsive patient demonstrated activity in brain regions associated with motor function when asked to imagine playing tennis, and activity in regions associated with spatial processing when asked to imagine navigating her house.[23] Since then, both task-based fMRI and electroencephalography (EEG) have been used to detect volitional modulation of brain activity, revealing CMD in up to 20% of behaviorally unresponsive patients.[24,25] Accordingly, international guidelines[4,5] and expert consensus statements[7] have endorsed the clinical use of technologies such as task-based fMRI and EEG to detect CMD. Clinicians may be particularly attuned to the possibility of CMD in patients with lesions of the anterior forebrain mesocircuit (eg, the globus pallidus and putamen), which have been associated with an increased incidence of CMD.[26]

Beyond identifying evidence of command following, emerging neurotechnologies have revealed additional physiological markers of preserved brain function in patients who appear unconscious. In acute and chronic settings, a subset of behaviorally unresponsive patients demonstrate preserved cortical responses to spoken language as measured with stimulus-based fMRI[27-30] or EEG[29,31,32] (ie, covert cortical processing),[8] preserved cortical metabolism as measured by positron emission tomography (PET),[33] or cortical activity as measured by the perturbational complexity index (PCI), which reflects the complexity of an EEG response to a pulse of transcranial magnetic stimulation (TMS).[34-36] While these physiological measures do not prove the presence of consciousness, they suggest that consciousness may be possible in another subset of patients previously presumed unaware, beyond those with CMD. As such, technologies such as PET and TMS-EEG have been endorsed by clinical guidelines as supplemental evaluations in the determination of consciousness.[4]

Findings from these emerging technologies suggest that the existing behavioral classification scheme of DoC (**Figure 4**A) may be insufficient. One approach is to incorporate new technologically defined categories into the existing scheme. For example, MCS star (MCS*) has been proposed to describe behaviorally unresponsive patients with cerebral metabolism consistent with the MCS.[33] A second approach is to consider forms of overt consciousness (assessed with conventional categories) and covert consciousness (assessed with emerging technologies) along different dimensions (Figure 4B).[29] A third approach is to avoid confident determina-

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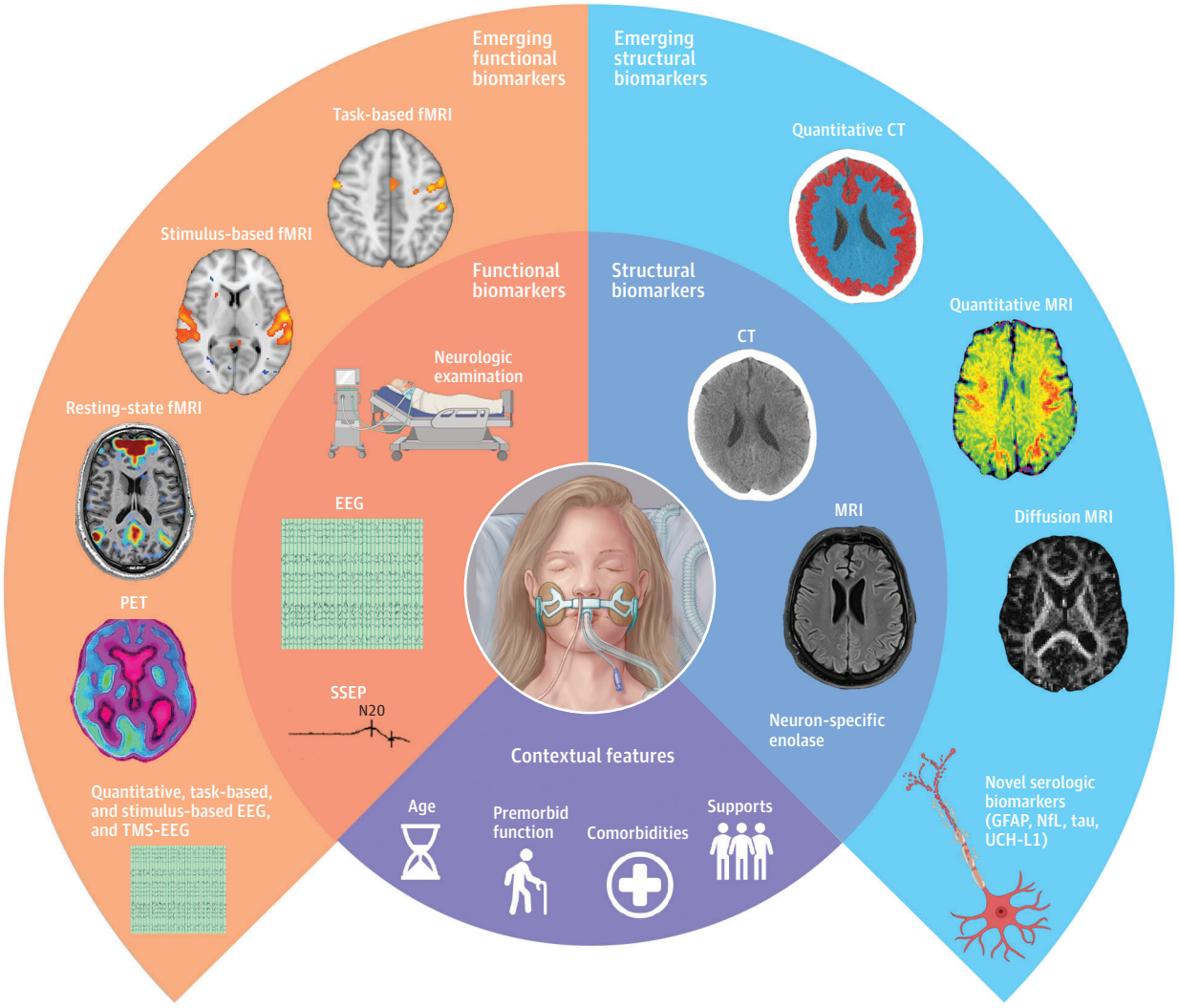
Figure 3. Prognostic Features and Markers



Anticipating a patient's capacity to recover neurologic function depends on markers that evaluate the functional integrity of the brain, markers that evaluate the structural integrity of the brain, and contextual features. There are conventional markers used for this purpose, as well as numerous emerging technologies that may improve the accuracy of these assessments. Parts of this figure were created with BioRender. CT indicates computed tomography; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; GFAP, glial fibrillary acidic protein; MRI, magnetic resonance imaging; NfL, neurofilament light; PET, positron emission tomography; SSEP, somatosensory evoked potentials; TMS, transcranial magnetic stimulation; UCH-L1, ubiquitin carboxyl hydrolase L1.

tions of consciousness[37,38] and to instead consider neurologic function along a single dimension that can be assessed with either behavioral or technological means (Figure 4C).[1,37] The notion of a composite reference standard for consciousness assessed by either behavioral or technological means has been endorsed by the European Academy of Neurology.[4]

Predicting Recovery With Multimodal Prognostic Markers

Once a patient's current level of consciousness, or neurologic function, has been characterized, the next step of neuroprognostication is to estimate the patient's likely trajectory of recovery (Figure 2B). While there are contextual features that influence recovery potential, eg, age, comorbidities, premorbid function, hospital complications, and brain injury etiology,[39-42] multimodal prognostic markers that assess functional and structural brain integrity are critical in this process. Because no prognostic marker has perfect accuracy, markers likely have greater predictive value when combined,[43] and thus guidelines urge clinicians to acquire multimodal assessments to more accurately predict recovery potential.[4] Here, we review the state of the science in functional and structural prognostic markers, emphasizing emerging techniques that may be translated to ICU care.

Studies of neuroprognostication operationalize outcomes heterogeneously but typically dichotomize functional scales into favorable and unfavorable outcomes, commonly defining the for-

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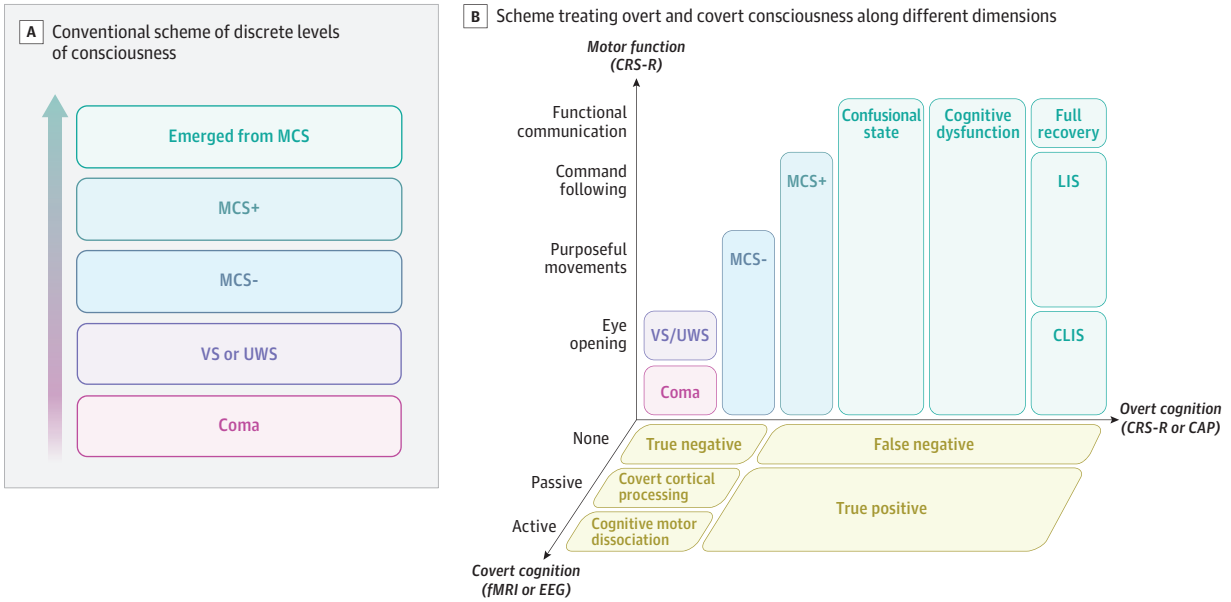
Figure 4. Schemes for Classifying Consciousness and Neurologic Function



C Scheme positing a single dimension of neurologic function

	Behavior	fMRI	EEG
Communicative Command or question (eg, "Move your hand")	Answers questions Follows commands	Modulates activity to answer questions Modulates activity to command	Modulates activity to answer questions Modulates activity to command
Responsive Noncommand stimulus (eg, "Once upon a time")	Reaches for objects Visually tracks target Movement prompted by stimulus	Complex activity evoked by stimulus Simple activity evoked by stimulus	Complex activity evoked by stimulus Simple activity evoked by stimulus
Spontaneous No stimulation	Spontaneous movements Spontaneous eye opening	Resting state network connectivity Spontaneous oscillations	Resting state network connectivity Spontaneous oscillations

A, The conventional scheme describes discrete levels of consciousness identified through behavior. B, An alternative scheme treats overt and covert consciousness along different dimensions. C, A third scheme posits a single dimension of neurologic function that can be evaluated with behavioral or technological means. CAP indicates Confusion Assessment Protocol; CLIS, complete locked-in syndrome; CRS-R, Coma Recovery Scale–Revised; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; LIS, locked-in syndrome; MCS, minimally conscious state; MCS+, minimally conscious state with language function; MCS−, minimally conscious state without language function; UWS, unresponsive wakefulness syndrome; VS, vegetative state.

mer by relative functional independence (eg, Cerebral Performance Category score ≤2,[44] modified Rankin Scale score ≤3,[45] or Glasgow Outcome Scale Extended score ≥4[46]).[47] Although such dichotomization undoubtedly oversimplifies the spectrum of acceptable recovery, for clarity here, allusions to a poor prognosis adhere to this convention unless otherwise specified.

Conventional Functional Markers

The first category of prognostic markers, which assess the functional integrity of the brain, uses many of the same techniques described above, but for the purpose of predicting future neurologic function rather than characterizing present neurologic function (**Table**). The most important functional prognostic marker in conventional practice is the neurologic examination, which has historically served as the bedrock of neuroprognostication. The first prognostically relevant aspect of the neurologic examination is the mental status. Traditional DoC categories not only characterize the patient's current level of consciousness but also predict future recovery: patients in an MCS typically achieve better functional outcomes at 1 year following their injury compared with those in a coma or VS/UWS.[55-57] Moreover, patients in an MCS+ at the time of admission to inpatient rehabilitation, compared with those in an MCS−, are less functionally impaired at discharge.[10] Other prognostically relevant examination features include brainstem reflexes, the absence of which portends a worse neurologic prognosis after injuries such as HIBI—an absent pupillary response more than 72 hours from the cardiac arrest remains among the most reliable predictors of a poor functional outcome.[6,47,50] Given subjectivity and error as-

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Table. Summary of Conventional and Emerging Prognostic Markers Across Brain Injury Etiologies

Marker type	HIBI		TBI	Intracranial hemorrhage	Ischemic stroke	Encephalitis	Toxic-metabolic
	Pre-TTM	Post-TTM					
Conventional functional markers							
Examination	Some examination features predictive (eg, myoclonic status epilepticus, absent brainstem reflexes, absent or extensor motor responses)[48,49]	Some examination features predictive (eg, absent pupillary or corneal reflexes >72 h after arrest)[6,47,48,50]	Some examination features may be predictive (eg, motor and pupillary responses)[51]	Some examination features may be predictive (eg, GCS score), but remains uncertain[52-54]	Not sufficiently studied	Not sufficiently studied	Not sufficiently studied
	MCS (particularly MCS+) achieves better neurologic outcomes than VS across traumatic and nontraumatic etiologies[55-57]						
EEG	Some EEG features predictive (eg, suppression, burst suppression)[49]	Some EEG features predictive (eg, suppression, burst suppression)[6,47,48,50]	Not sufficiently studied	Not sufficiently studied	Not sufficiently studied	Not sufficiently studied	Not sufficiently studied
SSEP	Bilaterally absent N20 responses predictive[49]	Bilaterally absent N20 responses predictive[6,47,48,50]	Bilaterally absent N20 responses may be predictive[58]	Not sufficiently studied	Not sufficiently studied	Not sufficiently studied	Not sufficiently studied
Emerging functional markers							
Emerging EEG	Task-based EEG,[59-61] stimulus-based EEG,[32,62] quantitative resting-state EEG,[63] and TMS-EEG[35,36] may be predictive in traumatic and nontraumatic etiologies; whether they extrapolate to all etiologies equally remains uncertain						
fMRI	Task-based fMRI,[64] stimulus-based fMRI,[27,28,30] resting-state fMRI,[65,66] and PET[33,64] may be predictive in traumatic and nontraumatic etiologies; whether they extrapolate to all etiologies equally remains uncertain						
Conventional structural markers							
CT	Not sufficiently studied[49]	Degree of gray vs white matter differentiation predictive[6,47,48,50]	Some features, such as edema and subarachnoid and intraventricular hemorrhage, may be predictive[42,51]	Location and size of intraparenchymal hemorrhage may be predictive,[67] although this remains uncertain[54]	Not sufficiently studied	Not sufficiently studied	Not sufficiently studied
MRI	Not sufficiently studied[49]	Degree of diffusion restriction predictive[6,47,48,50]	Extent of diffuse axonal injury may be predictive[68,69]	Location of intraparenchymal hemorrhage may be predictive,[70] although this remains uncertain[54]	Not sufficiently studied	Not sufficiently studied	Not sufficiently studied
NSE	NSE levels may be predictive[49]	NSE levels predictive but threshold uncertain[6,47,48,50]	Not sufficiently studied	Not sufficiently studied	Not sufficiently studied	Not sufficiently studied	Not sufficiently studied
Emerging structural markers							
Diffusion MRI	Not sufficiently studied	White matter fractional anisotropy may be predictive[71]	White matter fractional anisotropy may be predictive[72]	Not sufficiently studied	Not sufficiently studied	Not sufficiently studied	Not sufficiently studied
Emerging serologic markers	Not sufficiently studied[49]	Some (eg, neurofilament light) may be predictive[73]	Some (eg, neurofilament light) may be predictive[74]	Not sufficiently studied	Not sufficiently studied	Not sufficiently studied	Not sufficiently studied

Abbreviations: CT, computed tomography; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; GCS, Glasgow Coma Scale; HIBI, hypoxic-ischemic brain injury; MCS, minimally conscious state; MCS+, minimally conscious state with language function; MRI, magnetic resonance imaging; NSE, neuron-specific enolase; PET, positron emission tomography; SSEP, somatosensory evoked potentials; TBI, traumatic brain injury; TMS, transcranial magnetic stimulation; TTM, targeted temperature management; VS, vegetative state.

sociated with the conventional examination, quantification may improve prognostic accuracy; for example, quantitative pupillometry (which automatically detects and measures the pupillary light reflex) is superior to the conventional pupillary examination in predicting outcomes after HIBI.[6,75]

EEG represents another conventional functional prognostic marker and is typically used to evaluate cortical activity via scalp electrodes. Innumerable features of EEG have been investigated for prognostic value, and which features are most useful in each etiology of brain injury remains uncertain.[20,76,77] EEG has been studied most in HIBI, where a suppressed background or burst suppression (termed *highly malignant features*) reliably predicts poor functional recovery,[47,50] warranting inclusion in clinical guidelines.[6] Other EEG features that were historically believed to imply a poor prognosis, such as seizure or epileptiform discharges associated with myoclonus, have since been found to inconsistently predict prognosis.[47,50,78] Reactivity (a stimulus-induced change in EEG activity[79]), although among the less prognostically reliable EEG features,[47] has been associated with outcomes across injury etiologies, including HIBI, TBI, and intracranial hemorrhage.[80]

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Somatosensory evoked potentials (SSEPs) are conducted by stimulating a peripheral nerve and measuring the cortical response (termed the *N20*) or lack thereof. SSEPs have been studied most extensively in HIBI, where the absence of N20 responses to peripheral stimulation predicts poor neurologic outcomes.[7,47] (Of note, absent N20 responses are only prognostically meaningful if more distal responses [eg, at the brachial plexus] are preserved.) There has also been a growing interest in prognostic markers of favorable outcomes: for example, N20 responses with a high amplitude, or accompanied by high-frequency oscillations, have been associated with a more positive neurologic prognosis in HIBI.[81-83] SSEPs are endorsed by guidelines for HIBI,[6,50] but emerging evidence suggests that they may be prognostically relevant for predicting cognitive recovery in other etiologies, such as TBI, as well.[58]

Emerging Functional Markers

Emerging technologies offer additional insights into functional brain integrity in DoC. fMRI has been used in 3 forms: task-based fMRI (which assesses brain activity in response to commands), stimulus-based fMRI (in response to noncommand stimuli), and resting-state fMRI (in the absence of stimuli).[84] Task-based fMRI, which detects CMD (as described earlier), may have prognostic significance; in one study,[64] patients with CMD on task-based fMRI were more likely to recover overt signs of consciousness by 1 year following injury than those without. Stimulus-based fMRI may also have prognostic relevance; patients with cortical activation to auditory stimuli were more likely to recover consciousness and neurologic function than those without.[27,28] Activation of higher-level auditory cortices in response to language may predict a particularly robust functional recovery.[30]

Resting-state fMRI assesses functional brain integrity by measuring the synchronization of spontaneous activity between brain network regions. Greater synchronization (or functional connectivity) between regions indicates greater functional network integrity. Preserved integrity of networks, such as the default mode network, as well as preserved interactions between networks predict a greater likelihood of recovering consciousness and neurologic function.[43,65,66] Logistically, resting-state fMRI is simpler to acquire than other forms of fMRI, which require the delivery of stimuli.

Notably, the prognostic associations described for task-based fMRI, stimulus-based fMRI, and resting-state fMRI have been demonstrated across both traumatic and nontraumatic etiologies of DoC. Clinical guidelines released by the American Academy of Neurology, the American Congress of Rehabilitation Medicine, and the National Institute on Disability, Independent Living, and Rehabilitation Research have endorsed stimulus-based fMRI for clinical neuroprognostication, albeit with low confidence given the early stages of these technologies.[5]

Emerging methods of EEG acquisition and analysis have yielded novel insights into brain function in patients with DoC in acute and chronic settings. Whereas conventional EEG is typically interpreted subjectively, emerging techniques use quantitative interpretation (eg, machine learning) under task-based, stimulus-based, or resting-state conditions.[29,32,43,59,60] CMD detected with task-based EEG has prognostic significance, predicting greater neurologic function at 3 months[61] and 1 year (odds ratio, 4.6; 95% CI, 1.2-17.1)[59] following injury as well as a more rapid recovery[60] than patients without CMD. Stimulus-based EEG, which measures the cortical response to stimuli such as speech, also has prognostic significance; patients with cortical responses to stimuli, and particularly to more complex, syntactical features of language, were more likely to achieve greater neurologic function in the months following injury.[32,62] Quantitative analyses of resting-state EEG may also be prognostically relevant.[63] In one study,[85] graph theory metrics derived from high-density EEG were associated with outcomes at 1 year following injury. EEG can also be combined with TMS to determine the PCI (as described earlier), which may not only help determine a patient's current neurologic function but also predict consciousness recovery.[36] Like fMRI studies, studies of emerging EEG applications have shown prognostic relevance across both traumatic and nontraumatic etiologies of DoC.

PET has also been shown to predict recovery from DoC across a range of brain injury etiologies in acute and chronic settings. Patients with DoC but preserved cortical metabolism on PET are more likely to achieve a robust functional recovery at 1 year following injury than patients without similarly preserved metabolism.[33,64]

Conventional Structural Markers

The second category of prognostic markers assesses the brain's structural integrity (Table), for which conventional neuroimaging has been most used. Conventional neuroimaging techniques, and how they are interpreted, vary between brain injury etiologies. For etiologies that cause diffuse injury, the extent of injury tends to be prognostic. In HIBI treated with targeted temperature management (TTM), the extent to which the differentiation between gray and white matter is lost on computed tomography (CT) and the extent of diffusion restriction on MRI are both associated with prognosis.[6,47] Of note, head CT is more specific than sensitive,[86] and MRI is most sensitive and specific for prognosis on postarrest days 2 to 5.[87] In TBI, the extent of diffuse axonal injury (as estimated with MRI features such as microhemorrhages) and the extent of intracranial hemorrhage burden are associated with prognosis.[42,68,69] The prognostic implications of structural imaging of focal brain injury etiologies tend to depend on lesion locations. Focal lesions, such as ischemic stroke or intraparenchymal hemorrhage, that affect structures critical to arousal, such as the pontine tegmentum, are associated with more severe and prolonged disorders of consciousness.[70,88] However, recovery of consciousness and neurologic function is possible even after brainstem tegmentum lesions,[69,88] highlighting the potential for neuroplasticity and the importance of prognostic humility.

Serologic markers provide additional insight into the brain's structural integrity. Proteins and other markers contained within the neurovascular unit are released into the bloodstream during brain injury. As such, the serologic levels of these markers are thought to reflect the severity of neuronal injury. Neuron-specific enolase, an enzyme within neurons, is the serologic marker studied most extensively; in HIBI, higher levels of serologic neuron-specific enolase are associated with worse neurologic outcomes.[47] However, there is little consensus on the threshold appropriate for prognostication, and measurements may vary between assays, leading to inconsistent endorsement by clinical guidelines.[6,50]

Emerging Structural Markers

One advance in structural prognostic markers is the development of quantitative methods for analyzing conventional neuroimaging data. Although clinicians have long relied on CT and MRI as prog-

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nostic tools, qualitative assessment of these scans produces variable interpretations. For example, although the presence of HIBI on CT often influences clinical management (eg, withdrawal of LST), the interrater reliability of HIBI detection on CT is poor.[86] Thus, algorithms have been developed to automatically detect and compute the degree of injury identified with conventional imaging techniques. Algorithms that identify and quantify HIBI on CT[89] or MRI[90] have been shown to predict outcomes, in some cases with greater accuracy than conventional prognostic markers.

A second advance is the development of structural neuroimaging techniques that assess the integrity of neural networks. Diffusion MRI measures the movement of water molecules within brain tissue and provides a marker of axonal integrity through metrics such as fractional anisotropy—less uniform movement of water molecules along axonal tracts is thought to reflect injury to those tracts.[84] International, multicenter studies suggest that whole-brain white matter fractional anisotropy has prognostic relevance in both HIBI[71] and TBI,[72] where greater white matter integrity predicts better neurologic recovery. Diffusion MRI is also used for tractography, or 3-dimensional reconstruction of fiber bundles,[84] and limited evidence suggests that the integrity of these tracts in the acute setting may predict cognitive recovery after TBI.[91]

Novel serologic markers may have superior prognostic significance relative to conventional markers. The predictive values of S100 calcium-binding protein β (in glia), glial fibrillary acidic protein (in astrocytes), neurofilament light (in axons), tau (in axons), and ubiquitin carboxyl hydrolase L1 (in neuronal cell bodies) have been tested in ICU patients with acute HIBI, with markers such as neurofilament light demonstrating particular prognostic promise.[73] Emerging literature suggests that serologic markers such as neurofilament light may also predict outcomes in other etiologies of brain injury, such as TBI.[74]

Applying Multimodal Prognostic Markers to ICU Practice

When evaluating the clinical utility of any prognostic marker, several principles should be considered. A common metric of prognostic value is the false-positive rate (FPR), or the probability that a given marker may falsely predict a poor outcome.[48] Perhaps the direst risk of neuroprognostication is the erroneous withdrawal of LST due to an incorrectly presumed poor prognosis. Unlike the erroneous continuation of LST due to an incorrectly presumed favorable prognosis, the former error typically cannot be reversed. As such, avoiding the inaccurate prediction of a poor prognosis is prioritized, and thus a 0% FPR is the goal of any prognostic marker.[48] However, achievement of this goal may be limited by inherent testing error and bias.

There are several pitfalls and biases in the prognostication literature that render results difficult to interpret or translate into clinical practice. Among the most common is the self-fulfilling prophecy bias[92]: because clinicians are frequently not blinded to the prognostic markers being studied, predictions of a poor prognosis may lead to the withdrawal of LST, which produces a poor outcome and confirms the original predictions. For example, the intracerebral hemorrhage (ICH) score is sometimes used to predict mortality after ICH, but it includes mortality due to the withdrawal of LST[52]; after limiting withdrawal of LST, mortality rates decrease to approximately half of those predicted by the ICH score.[53] Thus, the FPR of any study that does not involve rigorous blinding must be interpreted with caution. Study heterogeneity also makes results difficult to translate: the aforementioned studies varied with respect to patient population, injury etiology, injury severity, acuity, technique details, outcome definitions, therapies (eg, with or without TTM in HIBI), and practices for withdrawing LST. Such heterogeneity likely contributes to variability observed between studies,[47] and extrapolation to any individual patient requires caution.

There are several additional considerations pertinent to the clinical application of prognostic data. First, the appropriate timing of neuroprognostication is often questioned. Given that prognostic markers may become more accurate with time (eg, examination and neuroimaging markers), some guidelines suggest waiting 72 hours after injury.[93] However, given that consciousness recovery may be more substantially delayed,[56,94] other guidelines suggest waiting at least 28 days after injury before confidently concluding a poor prognosis,[5] prompting more regular consideration of time-limited trials.[95] Second, when neuroprognostication is ultimately conducted to inform decisions about LST, clinicians not only must predict a patient's future neurologic function but also must consider what level of neurologic function would be acceptable to them.[1] To do so, clinicians must determine each patient's goals of care (Figure 2C), and because the care in question is often LST, such goals are typically defined as the minimum level of neurologic function that would make life worth living.[1] Although goals of care, and their evolution over time, can never be known with precise certainty,[96] clinicians may approximate those goals using at least 3 key sources: advance directives, surrogates, and population data.[1] Decision aids have been developed to help formulate patients' goals, which surrogates report as useful.[97,98] Once a patient's recovery trajectory is predicted and their goals of care are established, the final stage of neuroprognostication is to determine whether the chances and costs of reaching those goals, and therefore attaining a favorable outcome, justify the continuation or withdrawal of LST (Figure 2D).

Conclusions

Neuroprognostication is a high-stakes determination that often dictates whether LST is continued or withdrawn, yet it remains a major challenge. To best estimate the chances of recovery, clinicians draw on diverse prognostic data elements that reflect the patient's context, structural brain integrity, and functional brain integrity. As conventional prognostic markers remain imperfect, there are ongoing efforts to develop novel markers that improve the accuracy of neuroprognostication. Emerging functional prognostic markers, such as fMRI and advanced EEG, may further reveal a patient's current brain function and capacity for recovery. Emerging structural prognostic markers, such as quantitative neuroimaging, diffusion MRI, and novel serologic markers, may provide additional prognostic precision. Ensuring that the prognoses derived from these emerging markers continue to be coupled with individualized assessments of patient goals is critical to guiding sensitive decisions about LST.

There are many promising directions for the future of neuroprognostication research. Although guidelines have begun endorsing emerging prognostic markers for clinical use, translation is ham-

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pered by several factors: the techniques used to acquire and analyze emerging prognostic marker data have been variable, the equipment necessary for these techniques is often not widely available, and insurance may not provide necessary coverage. Further research to establish best practices and standards for emerging prognostic markers, to develop accessible methods for implementation, and to further establish the efficacy and cost-effectiveness of these techniques will be critical for their clinical translation.[96] As the neurobiology of consciousness continues to be elucidated,[99] biomarkers that provide more targeted assessments of these substrates, rather than of general neural integrity, may offer greater accuracy. Ultimately, elucidating these substrates may lead not only to more effective prognostic markers but also to targets for therapeutic modulation.[100]

Neuroprognostication is fraught with uncertainty. A portion of that uncertainty is unavoidable, attributable to inherent imprecision in identifying a patient's fundamentally subjective level of consciousness and in predicting the future. However, improvements in prognostic markers will hopefully lessen such uncertainty and allow critical decisions about LST to be made with greater clarity. Recognizing that the complex task of predicting consciousness recovery will likely never be made with certainty, clinicians should continue to approach these sensitive determinations with compassion and humility.

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REFERENCES

1. Fischer D, Edlow BL, Giacino JT, Greer DM. Neuroprognostication: a conceptual framework. *Nat Rev Neurol*. 2022;18(7):419-427. doi:10.1038/s41582-022-00644-7

2. Turgeon AF, Lauzier F, Burns KEA, et al; Canadian Critical Care Trials Group. Determination of neurologic prognosis and clinical decision making in adult patients with severe traumatic brain injury: a survey of Canadian intensivists, neurosurgeons, and neurologists. *Crit Care Med*. 2013;41(4):1086-1093. doi:10.1097/CCM.0b013e318275d046

3. Elmer J, Torres C, Aufderheide TP, et al; Resuscitation Outcomes Consortium. Association of early withdrawal of life-sustaining therapy for perceived neurological prognosis with mortality after cardiac arrest. *Resuscitation*. 2016;102:127-135. doi:10.1016/j.resuscitation.2016.01.016

4. Kondziella D, Bender A, Diserens K, et al; EAN Panel on Coma, Disorders of Consciousness. European Academy of Neurology guideline on the diagnosis of coma and other disorders of consciousness. *Eur J Neurol*. 2020;27(5):741-756. doi:10.1111/ene.14151

5. Giacino JT, Katz DI, Schiff ND, et al. Practice guideline update recommendations summary: disorders of consciousness: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research. *Neurology*. 2018;91(10):450-460. doi:10.1212/WNL.0000000000005926

6. Rajajee V, Muehlschlegel S, Wartenberg KE, et al. Guidelines for neuroprognostication in comatose adult survivors of cardiac arrest. *Neurocrit Care*. 2023;38(3):533-563. doi:10.1007/s12028-023-01688-3

7. Comanducci A, Boly M, Claassen J, et al. Clinical and advanced neurophysiology in the prognostic and diagnostic evaluation of disorders of consciousness: review of an IFCN-endorsed expert group. *Clin Neurophysiol*. 2020;131(11):2736-2765. doi:10.1016/j.clinph.2020.07.015

8. Edlow BL, Claassen J, Schiff ND, Greer DM. Recovery from disorders of consciousness: mechanisms, prognosis and emerging therapies. *Nat Rev Neurol*. 2021;17(3):135-156. doi:10.1038/s41582-020-00428-x

9. Kondziella D, Menon DK, Helbok R, et al; Contributing Collaborators of the Curing Coma Campaign. A precision medicine framework for classifying patients with disorders of consciousness: advanced classification of consciousness endotypes (ACCESS). *Neurocrit Care*. 2021;35(suppl 1):27-36. doi:10.1007/s12028-021-01246-9

10. Thibaut A, Bodien YG, Laureys S, Giacino JT. Minimally conscious state "plus": diagnostic criteria and relation to functional recovery. *J Neurol*. 2020;267(5):1245-1254. doi:10.1007/s00415-019-09628-y

11. Estraneo A, Moretta P, Loreto V, Lanzillo B, Santoro L, Trojano L. Late recovery after traumatic, anoxic, or hemorrhagic long-lasting vegetative state. *Neurology*. 2010;75(3):239-245. doi:10.1212/WNL.0b013e3181e8e8cc

12. Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil*. 2004;85(12):2020-2029. doi:10.1016/j.apmr.2004.02.033

13. Schnakers C, Vanhaudenhuyse A, Giacino J, et al. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. *BMC Neurol*. 2009;9(35):35. doi:10.1186/1471-2377-9-35

14. Bodien YG, Vora I, Barra A, et al. Feasibility and validity of the Coma Recovery Scale-Revised for Accelerated Standardized Testing: a practical assessment tool for detecting consciousness in the intensive care unit. *Ann Neurol*. 2023;94(5):919-924. doi:10.1002/ana.26740

15. Aubinet C, Cassol H, Bodart O, et al. Simplified Evaluation of Consciousness Disorders (SECONDs) in individuals with severe brain injury: a validation study. *Ann Phys Rehabil Med*. 2021;64(5):101432. doi:10.1016/j.rehab.2020.09.001

16. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet*. 1974;2(7872):81-84. doi:10.1016/S0140-6736(74)91639-0

17. Bodien YG, Barra A, Temkin NR, et al; TRACK-TBI Investigators. Diagnosing level of consciousness: the limits of the Glasgow Coma Scale total score. *J Neurotrauma*. 2021;38(23):3295-3305. doi:10.1089/neu.2021.0199

18. Wijdicks EFM, Bamlet WR, Maramattom BV, Manno EM, McClelland RL. Validation of a new coma scale: the FOUR score. *Ann Neurol*. 2005;58(4):585-593. doi:10.1002/ana.20611

19. Pincherle A, Jöhr J, Chatelle C, et al. Motor behavior unmasks residual cognition in disorders of consciousness. *Ann Neurol*. 2019;85(3):443-447. doi:10.1002/ana.25417

20. Curley WH, Bodien YG, Zhou DW, et al. Electrophysiological correlates of thalamocortical function in acute severe traumatic brain injury. *Cortex*. 2022;152:136-152. doi:10.1016/j.cortex.2022.04.007

21. Wannez S, Heine L, Thonnard M, Gosseries O, Laureys S; Coma Science Group Collaborators. The repetition of behavioral assessments in diagnosis of disorders of consciousness. *Ann Neurol*. 2017;81(6):883-889. doi:10.1002/ana.24962

22. Schiff ND. Cognitive motor dissociation following severe brain injuries. *JAMA Neurol*. 2015;72(12):1413-1415. doi:10.1001/jamaneurol.2015.2899

23. Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD. Detecting awareness in the vegetative state. *Science*. 2006;313(5792):1402. doi:10.1126/science.1130197

24. Kondziella D, Friberg CK, Frokjaer VG, Fabricius M, Møller K. Preserved consciousness in vegetative and minimal conscious states: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2016;87(5):485-492. doi:10.1136/jnnp-2015-310958

25. Schnakers C, Hirsch M, Noé E, et al. Covert cognition in disorders of consciousness: a meta-analysis. *Brain Sci*. 2020;10(12):1-11. doi:10.3390/brainsci10120930

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26. Franzova E, Shen Q, Doyle K, et al. Injury patterns associated with cognitive motor dissociation. *Brain*. 2023;146(11):4645-4658. doi:10.1093/brain/awad197

27. Coleman MR, Davis MH, Rodd JM, et al. Towards the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness. *Brain*. 2009;132(pt 9):2541-2552. doi:10.1093/brain/awp183

28. Wang F, Di H, Hu X, et al. Cerebral response to subject's own name showed high prognostic value in traumatic vegetative state. *BMC Med*. 2015;13(1):83. doi:10.1186/s12916-015-0330-7

29. Edlow BL, Chatelle C, Spencer CA, et al. Early detection of consciousness in patients with acute severe traumatic brain injury. *Brain*. 2017;140(9):2399-2414. doi:10.1093/brain/awx176

30. Norton L, Kazazian K, Gofton T, et al. Functional neuroimaging as an assessment tool in critically ill patients. *Ann Neurol*. 2023;93(1):131-141. doi:10.1002/ana.26530

31. Braiman C, Fridman EA, Conte MM, et al. Cortical response to the natural speech envelope correlates with neuroimaging evidence of cognition in severe brain injury. *Curr Biol*. 2018;28(23):3833-3839.e3. doi:10.1016/j.cub.2018.10.057

32. Sokoliuk R, Degano G, Banellis L, et al. Covert speech comprehension predicts recovery from acute unresponsive states. *Ann Neurol*. 2021;89(4):646-656. doi:10.1002/ana.25995

33. Thibaut A, Panda R, Annen J, et al. Preservation of brain activity in unresponsive patients identifies MCS star. *Ann Neurol*. 2021;90(1):89-100. doi:10.1002/ana.26095

34. Rosanova M, Gosseries O, Casarotto S, et al. Recovery of cortical effective connectivity and recovery of consciousness in vegetative patients. *Brain*. 2012;135(pt 4):1308-1320. doi:10.1093/brain/awr340

35. Casali AG, Gosseries O, Rosanova M, et al. A theoretically based index of consciousness independent of sensory processing and behavior. *Sci Transl Med*. 2013;5(198):198ra105. doi:10.1126/scitranslmed.3006294

36. Casarotto S, Comanducci A, Rosanova M, et al. Stratification of unresponsive patients by an independently validated index of brain complexity. *Ann Neurol*. 2016;80(5):718-729. doi:10.1002/ana.24779

37. Fischer DB, Truog RD. What is a reflex? a guide for understanding disorders of consciousness. *Neurology*. 2015;85(6):543-548. doi:10.1212/WNL.0000000000001748

38. Fischer D, Truog RD. The problems with fixating on consciousness in disorders of consciousness. *Am J Bioeth Neurosci*. 2017;8(3):135-140. doi:10.1080/21507740.2017.1366577

39. Murray GD, Butcher I, McHugh GS, et al. Multivariable prognostic analysis in traumatic brain injury: results from the IMPACT study. *J Neurotrauma*. 2007;24(2):329-337. doi:10.1089/neu.2006.0035

40. Xiong C, Hanafy S, Chan V, et al. Comorbidity in adults with traumatic brain injury and all-cause mortality: a systematic review. *BMJ Open*. 2019;9(11):e029072. doi:10.1136/bmjopen-2019-029072

41. Kowalski RG, Hammond FM, Weintraub AH, et al. Recovery of consciousness and functional outcome in moderate and severe traumatic brain injury. *JAMA Neurol*. 2021;78(5):548-557. doi:10.1001/jamaneurol.2021.0084

42. Snider SB, Temkin NR, Barber J, et al; TRACK-TBI Investigators. Predicting functional dependency in patients with disorders of consciousness: a TBI-Model Systems and TRACK-TBI study. *Ann Neurol*. 2023;94(6):1008-1023. doi:10.1002/ana.26741

43. Amiri M, Raimondo F, Fisher PM, et al. Multimodal prediction of 3- and 12-month outcomes in ICU patients with acute disorders of consciousness. *Neurocrit Care*. Published online September 11, 2023. doi:10.1007/s12028-023-01816-z

44. Mak M, Moulaert VRM, Pijls RW, Verbunt JA. Measuring outcome after cardiac arrest: construct validity of Cerebral Performance Category. *Resuscitation*. 2016;100(100):6-10. doi:10.1016/j.resuscitation.2015.12.005

45. Quinn TJ, Dawson J, Walters MR, Lees KR. Reliability of the modified Rankin Scale: a systematic review. *Stroke*. 2009;40(10):3393-3395. doi:10.1161/STROKEAHA.109.557256

46. Wilson JTL, Pettigrew LEL, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. *J Neurotrauma*. 1998;15(8):573-585. doi:10.1089/neu.1998.15.573

47. Sandroni C, D'Arrigo S, Cacciola S, et al. Prediction of poor neurological outcome in comatose survivors of cardiac arrest: a systematic review. *Intensive Care Med*. 2020;46(10):1803-1851. doi:10.1007/s00134-020-06198-w

48. Greer DM, Rosenthal ES, Wu O. Neuroprognostication of hypoxic-ischaemic coma in the therapeutic hypothermia era. *Nat Rev Neurol*. 2014;10(4):190-203. doi:10.1038/nrneurol.2014.36

49. Wijdicks EFM, Hijdra A, Young GB, Bassetti CL, Wiebe S; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2006;67(2):203-210. doi:10.1212/01.wnl.0000227183.21314.cd

50. Nolan JP, Sandroni C, Böttiger BW, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. *Resuscitation*. 2021;161:220-269. doi:10.1016/j.resuscitation.2021.02.012

51. Steyerberg EW, Mushkudiani N, Perel P, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. *PLoS Med*. 2008;5(8):e165. doi:10.1371/journal.pmed.0050165

52. Hemphill JC III, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke*. 2001;32(4):891-897. doi:10.1161/01.STR.32.4.891

53. Morgenstern LB, Zahuranec DB, Sánchez BN, et al. Full medical support for intracerebral hemorrhage. *Neurology*. 2015;84(17):1739-1744. doi:10.1212/WNL.0000000000001525

54. Hwang DY, Kim KS, Muehlschlegel S, et al. Guidelines for neuroprognostication in critically ill adults with intracerebral hemorrhage. *Neurocrit Care*. Published online November 3, 2023. doi:10.1007/s12028-023-01854-7

55. Giacino J, Kalmar K. The vegetative and minimally conscious states: a comparison of clinical features and functional outcome. *J Head Trauma Rehabil*. 1997;12(4):36-51. doi:10.1097/00001199-199708000-00005

56. Katz DI, Polyak M, Coughlan D, Nichols M, Roche A. Natural history of recovery from brain injury after prolonged disorders of consciousness: outcome of patients admitted to inpatient rehabilitation with 1-4 year follow-up. *Prog Brain Res*. 2009;177(C):73-88. doi:10.1016/S0079-6123(09)17707-5

57. Faugeras F, Rohaut B, Valente M, et al. Survival and consciousness recovery are better in the minimally conscious state than in the vegetative state. *Brain Inj*. 2018;32(1):72-77. doi:10.1080/02699052.2017.1364421

58. Houlden DA, Taylor AB, Feinstein A, et al. Early somatosensory evoked potential grades in comatose traumatic brain injury patients predict cognitive and functional outcome. *Crit Care Med*. 2010;38(1):167-174. doi:10.1097/CCM.0b013e3181c031b3

59. Claassen J, Doyle K, Matory A, et al. Detection of brain activation in unresponsive patients with acute brain injury. *N Engl J Med*. 2019;380(26):2497-2505. doi:10.1056/NEJMoa1812757

60. Egbebike J, Shen Q, Doyle K, et al. Cognitive-motor dissociation and time to functional recovery in patients with acute brain injury in the USA: a prospective observational cohort study. *Lancet Neurol*. 2022;21(8):704-713. doi:10.1016/S1474-4422(22)00212-5

61. Pan J, Xie Q, Qin P, et al. Prognosis for patients with cognitive motor dissociation identified by brain-computer interface. *Brain*. 2020;143(4):1177-1189. doi:10.1093/brain/awaa026

62. Ling Y, Xu C, Wen X, Li J, Gao J, Luo B. Cortical responses to auditory stimulation predict the prognosis of patients with disorders of consciousness. *Clin Neurophysiol*. 2023;153:11-20. doi:10.1016/j.clinph.2023.06.002

63. Bouchereau E, Marchi A, Hermann B, et al. Quantitative analysis of early-stage EEG reactivity predicts awakening and recovery of consciousness in patients with severe brain injury. *Br J Anaesth*. 2023;130(2):e225-e232. doi:10.1016/j.bja.2022.09.005

64. Stender J, Gosseries O, Bruno MA, et al. Diagnostic precision of PET imaging and functional MRI in disorders of consciousness: a clinical validation study. *Lancet*. 2014;384(9942):514-522. doi:10.1016/S0140-6736(14)60042-8

65. Sair HI, Hannawi Y, Li S, et al; Neuroimaging for Coma Emergence and Recovery (NICER) Consortium. Early functional connectome integrity and 1-year recovery in comatose survivors of cardiac arrest. *Radiology*. 2018;287(1):247-255. doi:10.1148/radiol.2017162161

66. Amiri M, Fisher PM, Raimondo F, et al. Multimodal prediction of residual consciousness in the intensive care unit: the CONNECT-ME study. *Brain*. 2023;146(1):50-64. doi:10.1093/brain/awac335

67. Hwang DY, Dell CA, Sparks MJ, et al. Clinician judgment vs formal scales for predicting intracerebral hemorrhage outcomes. *Neurology*.

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2016;86(2):126-133. doi:10.1212/WNL.0000000000002266

68. Haghbayan H, Boutin A, Laflamme M, et al. The prognostic value of MRI in moderate and severe traumatic brain injury: a systematic review and meta-analysis. *Crit Care Med*. 2017;45(12):e1280-e1288. doi:10.1097/CCM.0000000000002731

69. Bianciardi M, Izzy S, Rosen BR, Wald LL, Edlow BL. Location of subcortical microbleeds and recovery of consciousness after severe traumatic brain injury. *Neurology*. 2021;97(2):e113-e123. doi:10.1212/WNL.0000000000012192

70. Rohaut B, Doyle KW, Reynolds AS, et al. Deep structural brain lesions associated with consciousness impairment early after hemorrhagic stroke. *Sci Rep*. 2019;9(1):4174. doi:10.1038/s41598-019-41042-2

71. Velly L, Perlbarg V, Boulier T, et al; MRI-COMA Investigators. Use of brain diffusion tensor imaging for the prediction of long-term neurological outcomes in patients after cardiac arrest: a multicentre, international, prospective, observational, cohort study. *Lancet Neurol*. 2018;17(4):317-326. doi:10.1016/S1474-4422(18)30027-9

72. Puybasset L, Perlbarg V, Unrug J, et al; MRI-COMA Investigators CENTER-TBI MRI Participants and MRI Only Investigators. Prognostic value of global deep white matter DTI metrics for 1-year outcome prediction in ICU traumatic brain injury patients: an MRI-COMA and CENTER-TBI combined study. *Intensive Care Med*. 2022;48(2):201-212. doi:10.1007/s00134-021-06583-z

73. Hoiland RL, Rikhraj KJK, Thiara S, et al. Neurologic prognostication after cardiac arrest using brain biomarkers: a systematic review and meta-analysis. *JAMA Neurol*. 2022;79(4):390-398. doi:10.1001/jamaneurol.2021.5598

74. Shahim P, Gren M, Liman V, et al. Serum neurofilament light protein predicts clinical outcome in traumatic brain injury. *Sci Rep*. 2016;6:36791. doi:10.1038/srep36791

75. Solari D, Rossetti AO, Carteron L, et al. Early prediction of coma recovery after cardiac arrest with blinded pupillometry. *Ann Neurol*. 2017;81(6):804-810. doi:10.1002/ana.24943

76. Engemann DA, Raimondo F, King JR, et al. Robust EEG-based cross-site and cross-protocol classification of states of consciousness. *Brain*. 2018;141(11):3179-3192. doi:10.1093/brain/awy251

77. Forgacs PB, Devinsky O, Schiff ND. Independent functional outcomes after prolonged coma following cardiac arrest: a mechanistic hypothesis. *Ann Neurol*. 2020;87(4):618-632. doi:10.1002/ana.25690

78. Elmer J, Rittenberger JC, Faro J, et al; Pittsburgh Post-Cardiac Arrest Service. Clinically distinct electroencephalographic phenotypes of early myoclonus after cardiac arrest. *Ann Neurol*. 2016;80(2):175-184. doi:10.1002/ana.24697

79. Hirsch LJ, Fong MWK, Leitinger M, et al. American Clinical Neurophysiology Society's standardized critical care EEG terminology: 2021 version. *J Clin Neurophysiol*. 2021;38(1):1-29. doi:10.1097/WNP.0000000000000806

80. Synek VM. Prognostically important EEG coma patterns in diffuse anoxic and traumatic encephalopathies in adults. *J Clin Neurophysiol*. 1988;5(2):161-174. doi:10.1097/00004691-198804000-00003

81. Sandroni C, D'Arrigo S, Cacciola S, et al. Prediction of good neurological outcome in comatose survivors of cardiac arrest: a systematic review. *Intensive Care Med*. 2022;48(4):389-413. doi:10.1007/s00134-022-06618-z

82. Scarpino M, Lolli F, Lanzo G, et al; ProNeCA Study Group. SSEP amplitude accurately predicts both good and poor neurological outcome early after cardiac arrest: a post-hoc analysis of the ProNeCA multicentre study. *Resuscitation*. 2021;163:162-171. doi:10.1016/j.resuscitation.2021.03.028

83. Endisch C, Waterstraat G, Storm C, Ploner CJ, Curio G, Leithner C. Cortical somatosensory evoked high-frequency (600Hz) oscillations predict absence of severe hypoxic encephalopathy after resuscitation. *Clin Neurophysiol*. 2016;127(7):2561-2569. doi:10.1016/j.clinph.2016.04.014

84. Fischer D, Newcombe V, Fernandez-Espejo D, Snider SB. Applications of advanced MRI to disorders of consciousness. *Semin Neurol*. 2022;42(3):325-334. doi:10.1055/a-1892-1894

85. Chennu S, Annen J, Wannez S, et al. Brain networks predict metabolism, diagnosis and prognosis at the bedside in disorders of consciousness. *Brain*. 2017;140(8):2120-2132. doi:10.1093/brain/awx163

86. Beekman R, Maciel CB, Ormseth CH, et al. Early head CT in post-cardiac arrest patients: a helpful tool or contributor to self-fulfilling prophecy? *Resuscitation*. 2021;165:68-76. doi:10.1016/j.resuscitation.2021.06.004

87. Wijman CAC, Mlynash M, Caulfield AF, et al. Prognostic value of brain diffusion-weighted imaging after cardiac arrest. *Ann Neurol*. 2009;65(4):394-402. doi:10.1002/ana.21632

88. Fischer DB, Boes AD, Demertzi A, et al. A human brain network derived from coma-causing brainstem lesions. *Neurology*. 2016;87(23):2427-2434. doi:10.1212/WNL.0000000000003404

89. Wu O, Batista LM, Lima FO, Vangel MG, Furie KL, Greer DM. Predicting clinical outcome in comatose cardiac arrest patients using early noncontrast computed tomography. *Stroke*. 2011;42(4):985-992. doi:10.1161/STROKEAHA.110.594879

90. Wouters A, Scheldeman L, Plessers S, et al. Added value of quantitative apparent diffusion coefficient values for neuroprognostication after cardiac arrest. *Neurology*. 2021;96(21):e2611-e2618. doi:10.1212/WNL.0000000000011991

91. Wang JY, Bakhadirov K, Abdi H, et al. Longitudinal changes of structural connectivity in traumatic axonal injury. *Neurology*. 2011;77(9):818-826. doi:10.1212/WNL.0b013e31822c61d7

92. Geocadin RG, Peberdy MA, Lazar RM. Poor survival after cardiac arrest resuscitation: a self-fulfilling prophecy or biologic destiny? *Crit Care Med*. 2012;40(3):979-980. doi:10.1097/CCM.0b013e3182410146

93. Souter MJ, Blissitt PA, Blosser S, et al. Recommendations for the critical care management of devastating brain injury: prognostication, psychosocial, and ethical management: a position statement for healthcare professionals from the Neurocritical Care Society. *Neurocrit Care*. 2015;23(1):4-13. doi:10.1007/s12028-015-0137-6

94. McCrea MA, Giacino JT, Barber J, et al; TRACK-TBI Investigators. Functional outcomes over the first year after moderate to severe traumatic brain injury in the prospective, longitudinal TRACK-TBI Study. *JAMA Neurol*. 2021;78(8):982-992. doi:10.1001/jamaneurol.2021.2043

95. Miranda SP, Morris RS, Rabas M, Creutzfeldt CJ, Cooper Z. Early shared decision-making for older adults with traumatic brain injury: using time-limited trials and understanding their limitations. *Neurocrit Care*. 2023;39(2):284-293. doi:10.1007/s12028-023-01764-8

96. Claassen J, Kondziella D, Alkhachroum A, et al; Curing Coma Campaign, and Its Contributing Collaborators. Cognitive motor dissociation: gap analysis and future directions. *Neurocrit Care*. Published online June 22, 2023. doi:10.1007/s12028-023-01769-3

97. Muehlschlegel S, Hwang DY, Flahive J, et al. Goals-of-care decision aid for critically ill patients with TBI: development and feasibility testing. *Neurology*. 2020;95(2):e179-e193. doi:10.1212/WNL.0000000000009770

98. Muehlschlegel S, Goostrey K, Flahive J, Zhang Q, Pach JJ, Hwang DY. Pilot randomized clinical trial of a goals-of-care decision aid for surrogates of patients with severe acute brain injury patients. *Neurology*. 2022;99(14):e1446-e1455. doi:10.1212/WNL.0000000000200937

99. Koch C, Massimini M, Boly M, Tononi G. Neural correlates of consciousness: progress and problems. *Nat Rev Neurosci*. 2016;17(5):307-321. doi:10.1038/nrn.2016.22

100. Edlow BL, Barra ME, Zhou DW, et al. Personalized connectome mapping to guide targeted therapy and promote recovery of consciousness in the intensive care unit. *Neurocrit Care*. 2020;33(2):364-375. doi:10.1007/s12028-020-01062-7

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